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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/945,459	12/09/1997	FUSAO MAKISHIMA	146.1275	2741

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	08/945,459	MAKISHIMA ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 February 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *26 November 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *49-66*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

David S Romeo
Primary Examiner
Art Unit: 1647

Continuation of 5. does NOT place the application in condition for allowance because: The amendment filed 02/17/2004 has been entered. Claims 49-66 are pending.

New claim 49 (Old Claim 17) is rejected under 35 U.S.C. 103(a) as being unpatentable over Celeste (a10) in view of Ben-Bassat (w10), Hirel (u20), and Georgiou (x13) and further in view of Tonouchi (y13) and Thompson (a27).

New claims 49, 50 (Old Claims 17, 18) are rejected under 35 U.S.C. 103(a) as being unpatentable over Celeste (a10) in view of Ben-Bassat (w10), Hirel (u20), and Georgiou (x13) and further in view of Tonouchi (y13) and Thompson (a27) as applied to new claim 49 (old claim 17) above and further in view of Hotten (2, cited by Applicants) and Cerletti (n10).

New claims 49-66 (Old Claims 17-28, 41-47) are rejected under 35 U.S.C. 103(a) as being unpatentable over Celeste (a10) in view of Ben-Bassat (w10), Hirel (u20), and Georgiou (x13) and further in view of Tonouchi (y13) and Thompson (a27) as applied to new claim 49 (Old claim 17) above and further in view of Hotten (2, cited by Applicants) and Cerletti (n10) as applied to new claim 50 (old claim 18) above and further in view of Neidhardt (1, cited by Applicants).

Applicants argue that Celeste was not able to show activity for MP52 and, therefore, the skilled artisan would not reasonably believe that shorter fragments of MP52 would show sufficient application in vivo. Applicant's arguments have been fully considered but they are not persuasive. The lack of results seen with MP52 in Celeste's assay can be attributed to the particular assay conditions used by Celeste because the effects of rhGDF-5/MP52 are dependent upon the amount of MP52 and the assay conditions, as evidenced in the last Office action. Regardless of the lack of an effect of MP52, it remains that a chemical composition and its properties are inseparable. Therefore, the properties applicant discloses and/or claims, i.e. "has cartilage and/or bone morphogenetic activity", are necessarily present in the protein taught by the cited prior art. Nor are these properties, i.e. "cartilage and/or bone morphogenetic activity", unexpected because the present specification at page 2, lines 1-3, discloses that the bone morphogenetic activity of MP52 has been reported. Furthermore, Hotten (a37) discloses that in both experimental animals considerable formation of cartilage and bone was detected in the implants containing [2 to 4 micrograms] MP52. The corresponding implants with control protein showed no formation whatsoever of cartilage or bone. See column 14, lines 60-64. This response was confirmed in two different assays. See column 16, full paragraph 1, "These results also confirm that MP52 can induce endochondral bone formation." Thus, the cartilage and/or bone morphogenetic activity of MP52 was known at the time of Applicants' invention.

Applicants argue that one skilled in the art would believe that deleting basic amino acids within the N-terminus would result in decreased interactions with the ECM in vivo, which would mean that higher concentrations of MP52 would have to be administered. Applicants argue that it was not predictable that the shortened fragments would remain at the site long enough in vivo. Applicants argue that one cannot assume that that shortened forms of MP52 would retain the same biological activity as the non-shortened forms because the effect of the accumulation of basic amino acids was not yet known. Applicant argues that considerable effort would be required the skilled artisan to determine the conditions required for the in vivo activity for MP52 and shortened fragments thereof. Applicants argue that the skilled artisan would not assume that changes can generally be made at the N-terminus without affecting interaction with the ECM and thus changing activity. Applicant's arguments have been fully considered but they are not persuasive. Although shortened forms of MP52 might not be as active as the full-length mature form, Celeste is evidence that one of ordinary skill in the art would nevertheless still expect them to be active. Furthermore, the shortened form of MP52 taught by the cited prior in the present rejection only teaches shortening the native full-length mature MP52 by deleting a single Ala residue at the N-terminus. Thus, the shortened form of MP52 taught by the cited prior in the present rejection retains its full complement of ECM-interacting basic amino acids. Therefore, according to Applicants' arguments, one of ordinary skill in the art would expect the shortened form of MP52 taught by the cited prior in the present rejection to be as ECM-interacting as the full length mature form of MP52. Applicants' arguments regarding the deletion of basic amino acid residues in the N-terminus of MP52 are not persuasive because the amino acid residue Ala, which is deleted following the teachings of the prior art in the present rejection, is not a basic amino acid.

Applicants argue that Celeste does not disclose or suggest the appropriate dosages for activity with an MP52 fragments starting with amino acid 17 or 19. Applicant's arguments have been fully considered but they are not persuasive. Neidhardt teaches a pharmaceutical composition comprising MP52 and a pharmaceutically acceptable carrier for use in the healing of bone, cartilage, or tooth defects (page 9, full paragraph 1), and it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a pharmaceutical composition comprising an amount of a native biologically active dimer of a protein consisting of the 119 amino acids as shown in SEQ ID NO: 1 without residual proteins effective for the healing of bone and/or cartilage with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to make a composition suitable for the healing of bone and/or cartilage. The examiner has interpreted an amount effective to heal bone and/or cartilage as an amount effective to treat the recited cartilage and/or bone diseases.

Applicants referral to the previously submitted Ohkawara article is acknowledged. However, the examiner cannot find such an article in any of the prior art documents of record in the present application. To the extent that Applicants rely upon this article for a teaching that changes in the N-terminus cannot be made without affecting activity, Applicant's arguments have been fully considered but they are not persuasive because the shortened form of MP52 taught by the cited prior in the present rejection only teaches shortening the native full-length mature MP52 by deleting a single Ala residue at the N-terminus and is not concerned with the deletion or addition of basic amino acid residues. Furthermore, one of ordinary skill in the art would reasonably expect this shortened form to retain activity, as evidenced by Celeste.